

## REMARKS

In the December 16, 2003 Office Action, the Examiner rejected claims 31, 33, 40, and 48-50 pending in the application. This Response amends claims 31 and 48 for further consideration. After entry of the foregoing amendments, claims 31, 33, 40, and 48-50 (two independent claims; six total claims) remain pending in the application. Reconsideration is respectfully requested.

Claims 31, 33 and 40 stand rejected under 35 U.S.C. §102(b) as being anticipated by either Gaskell and Brownsey (Clin. Chem., 29(4): 677-680, 1983), Gaskell (Steroids, 55: 458-462, 1990), Bonfanti (Cancer Research, 50: 68706875, 1990) or Davoli (Anal. Chem., 65: 2679-2685, 1993). Applicants respectfully traverse this rejection.

In particular, with respect to the Gaskell and Brownsey reference, the Examiner states that Gaskell and Brownsey teach a method for quantifying estradiol-17 $\beta$ , where a deuterated estradiol internal standard is added to a plasma sample, mixing a solid-phase coupled antiserum specific for both the labeled and unlabeled estradiol, and then drying and analyzing the extract using gas chromatography (GC)-mass spectrometry (MS). The Examiner further states that the ratios of the estradiol to deuterated estradiol are compared to a standard curve for quantification.

The Gaskell and Brownsey reference teaches away from Applicants' invention by requiring an additional step for analysis, namely a chromatographic step between affinity capture and mass spectrometry. The additional chromatography step utilized in Gaskell and Brownsey has the potential to introduce errors in the analysis by shifting retention times of the analyte and its deuterated isoform. Further, unlike Applicants' claimed method, the Gaskell and Brownsey reference fails to monitor the ion signals from both the analyte and the IRS in the same mass spectrum. Instead, a peak-switching approach is used which selectively monitors only the analyte or the IRS within the eluate from the chromatographic column.

With respect to the 1990 Gaskell reference, the Examiner states that Gaskell teaches a method for quantifying DHA-S, where a deuterated DHA-S internal standard is added to a serum sample and then added to an immunoaffinity column. The Examiner further states that the immunoaffinity eluate is analyzed by gas-chromatography-mass spectrometry and that the ratios of the DHA-S and deuterated internal standard are compared to a standard curve for quantification.

The 1990 Gaskell reference discloses quantification of DHA-S in serum using fast atom bombardment (FAB)/tandem mass spectrometry. The quantification method includes: (1) stable isotope dilution using an internal standard, (2) isolation of the analyte by immunoadsorption, namely highly selective retention on a solid phase incorporating bound antiserum raised against a conjugate of DHA, and (3) detection of both analyte and internal standard during limited mass range parent ion scanning during tandem MS. (See page 460 of the reference). Accordingly, unlike the Examiner's assertion on page 3 of her office action, the Gaskell reference utilizes FAB/MS instead of GC-MS.

Nevertheless, the 1990 Gaskell reference also teaches away from Applicants' claimed invention by using tandem MS for quantification. In other words, different mass spectrometric measurements are taken of similar portions of the same serum extract and compared. (See page 461 of the reference). Unlike Applicants' claimed invention, the analyte and IRS are not measured using MS in a single measurement. In addition, the 1990 Gaskell reference also teaches away from Applicants' claimed invention by requiring multiple sample preparation steps in between extraction and mass spectrometry. (See pages 460-461 of the reference).

With respect to the Bonfanti reference, the Examiner contends that Bonfanti teaches a method for quantifying O<sup>6</sup>-butylguanine where a deuterated internal standard is added to a serum sample and then loaded onto an immunoaffinity column. The Examiner then states that the immunoaffinity column eluate is analyzed by GC-MS and that the ratios of the O<sup>6</sup>-butylguanine and deuterated internal standard are compared to a standard curve for quantification.

The Bonfanti reference essentially uses the same approach as the Gaskell and Brownsey reference previously discussed above. More specifically, the Bonfanti reference uses a methodological approach that involves different separation factors that include: "binding to an antibody, separation by high resolution gas chromatography, and detection of a specific ion in the mass spectrometer." Moreover, this reference specifically states that "the first separation factor is very important and has to be efficient, since high resolution gas chromatography-mass spectrometry has the serious drawback of requiring thorough purification procedures before sophisticated analysis. . . . The selectivity of the purification step by immunoaffinity chromatography depends on the specificity of the antibody employed." (See page 6872 of the reference).

Like the Gaskell and Brownsey reference, the Bonfanti reference teaches away from

Applicants' claimed invention by requiring an additional step for analysis, namely a chromatographic step between affinity capture and mass spectrometry. As previously stated, this additional chromatography step has the potential to introduce errors in the analysis by shifting retention times of the analyte and its deuterated isoform. Moreover, the Bonfanti reference fails to monitor both the analyte and the IRS in the same measurement using MS.

Finally, with respect to the Davoli reference, the Examiner contends that Davoli teaches a method for quantifying diethylstilbestrol where deuterated internal standards are added to urine samples that are loaded onto immunoaffinity columns. The Examiner further states that the eluate is analyzed by fast atom bombardment mass spectrometry and that quantification is made by comparison to a standard curve.

In the Davoli reference, extraction was done by injecting samples directly into an immunoaffinity column containing antidiethylstilbestrol antibodies bound to a Sepharose matrix, and analysis was done by on-line high-performance liquid chromatography with ultraviolet and continuous-flow fast atom bombardment mass spectrometry detectors. (See page 2681 of the reference). Once again, this reference also teaches away from Applicants' claimed invention by requiring additional analysis steps, namely high-performance liquid chromatography and fast atom bombardment in addition to MS. Once again, these additional steps create the possibility of introducing errors in the analysis. Moreover, unlike Applicants' claimed invention, Davoli selectively monitors only the analyte or the IRS when obtaining measurements. In Applicants' claimed invention, both the analyte and the IRS signal are measured in a single measurement.

Applicants' claimed invention overcomes potential problems in all of the prior art cited by the Examiner by measuring both the analyte and the IRS signal in a single measurement. Essentially, in Applicants' claimed invention, the mass spectrometry accomplishes both the separation and the mass measurement in a single step.

Claims 31, 33, 40, and 48-50 stand rejected under 35 U.S.C. §102(a) as being anticipated by Nelson (Nelson, R.W. et al., Anal. Chem. 67:1153-1158, 1995, April 1). More particularly, the Examiner states that Nelson appears to teach a method that is the same as that claimed by Applicants. The Examiner also notes that although the publication date of Nelson is less than one year from the effective filing date of the instant application, the authorship of the Nelson article falls under the category of "another inventor" because it names inventors that are not named as co-inventors in the instant application. Applicant respectfully traverses this rejection.

Under 35 U.S.C. §102(a), a person is entitled to a patent unless the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the Applicant for a patent. The Nelson journal article cited by the Examiner does not constitute a description of the invention in a printed publication before the invention was made by Applicants in that Applicants are the authors of the journal article and Applicants conceived their invention before the publication of their journal article.

It should be noted that Mr. Allan L. Bieber, who is also noted as an author of the Nelson reference did not take part in the conception of the subject matter disclosed and claimed in the instant application and instead provided materials for carrying out and performing experimental protocols that were determined by the inventors listed in the subject application. Mr. Bieber's declaration attesting to these facts is attached hereto. Accordingly, claims 31-34, 37-39, 41 and 44-47 are not anticipated by Nelson and Applicants respectfully request the withdrawal of the Examiner's rejection under 35 U.S.C. §102(a).

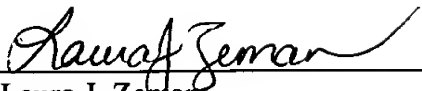
Finally, claims 31, 33, 40, and 48-50 stand rejected under 35 U.S.C. §102(b) as being anticipated by Lisek (Lisek, C.A. et al. Rapid Communications in Mass Spectrometry 3(2): 43-46, 1989; Abstract only). In particular, the Examiner states that Lisek teaches a method in which an amino acid peptide is mixed with a deuterated internal standard form of the amino acid peptide, applied to an immunoaffinity column and then analyzed by mass spectrometry. Applicant respectfully traverses this rejection.

Lisek, like the Gaskell and Brownsey reference and the Davoli reference, also teaches away from Applicants' claimed invention by requiring additional analysis steps, namely high-performance liquid chromatography and fast atom bombardment in addition to MS. Applicants' claims are directed to a method for quantifying an analyte where a specimen is combined with an affinity reagent to bind the analyte and an internal reference standard and the bound analyte is then analyzed and quantified using only mass spectrometry.

In view of the foregoing, Applicants respectfully submit that all of the pending claims fully comply with 35 U.S.C. §112 and are allowable over the prior art of record. Reconsideration of the application and allowance of all pending claims is earnestly solicited. Should the Examiner wish to discuss any of the above in greater detail or deem that further amendments should be made to improve the form of the claims, then the Examiner is invited to

telephone the undersigned at the Examiner's convenience.

Respectfully submitted,

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